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THE PRESENT AND FUTURE

JACC STATE-OF-THE-ART REVIEW

Peripartum Cardiomyopathy

JACC State-of-the-Art Review

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ABSTRACT

Peripartum cardiomyopathy is a form of systolic heart failure affecting young women toward the end of pregnancy or in the months following delivery. Incidence is higher in African-American women and in women with older maternal age, hypertensive disorders of pregnancy, and multiple gestation pregnancies. Symptoms of heart failure mimic those of normal pregnancy, often resulting in a delay in diagnosis and preventable complications. Echocardiography showing decreased myocardial function is essential for the diagnosis. Medical management is similar to heart failure with reduced ejection fraction of other etiologies, but adjustments during pregnancy are necessary to ensure fetal safety. Variable outcomes include complete recovery, persistent heart failure, arrhythmias, thromboembolic events, and death. Subsequent pregnancy confers substantial risk of relapse and even death if there is incomplete myocardial recovery. Additional research about the etiology, optimal therapy including the use of bromocriptine, long-term outcomes, and duration of treatment after recovery are needed. (J Am Coll Cardiol 2020;75:207–21) © 2020 by the American College of Cardiology Foundation.

Peripartum cardiomyopathy (PPCM) is a form of systolic heart failure (HF) with reduced left ventricular ejection fraction (LVEF) affecting childbearing women during pregnancy or in the early postpartum period. Delays in diagnosis may occur because the symptoms and signs of PPCM can mimic the normal findings of late pregnancy and the peripartum period. Although some women have relatively mild disease and complete recovery, others experience significant morbidity and mortality. This clinical review will describe the definition, risk factors, etiology, pathophysiology, and prognostic factors and will provide recommendations for diagnosis, acute and chronic management, and important counseling considerations, including breastfeeding and subsequent pregnancies.

DEFINITION

PPCM is a diagnosis of exclusion in women presenting with HF due to left ventricular (LV) systolic dysfunction and should be considered when no other cause is evident. PPCM was previously defined as symptomatic HF presenting in the last month of pregnancy and up to 5 months postpartum (1,2); however, the definition has been broadened because women who presented prior to the last month of gestation were found to be clinically indistinguishable from patients with classically-defined PPCM (3). The 2010 Heart Failure Association of the European Society of Cardiology Working Group therefore revised the definition of PPCM to "an idiopathic cardiomyopathy presenting with HF secondary to LV systolic dysfunction towards the end of pregnancy or

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ABBREVIATIONS AND ACRONYMS

ACE = angiotensin-converting enzyme

BNP = brain natriuretic peptide

DCM = dilated cardiomyopathy

HF = heart failure

ICD = implantable cardioverter-defibrillator

LV = left ventricular

LVAD = left ventricular assist device

LVEF = left ventricular ejection fraction

PPCM = peripartum cardiomyopathy

in the months following delivery, where no other cause of heart failure is found" (4). The diagnostic criteria indicate that LVEF is <45% and there may or may not be ventricular dilatation (4,5). Outcomes are variable; women may have complete recovery, persistent myocardial dysfunction and HF, or rapid deterioration, leading to urgent need for temporary or durable mechanical circulatory support and cardiac transplantation (**Central Illustration**).

HIGHLIGHTS

- Medications used to treat HF during pregnancy and lactation require special considerations.
- Severe HF may require advanced therapies and mechanical circulatory support.
- Subsequent pregnancies carry risk of relapse, and dedicated counseling and monitoring are essential.
- Future research about long-term outcomes, continued drug therapy, use of bromocriptine, device therapy, and genetics are needed.

EPIDEMIOLOGY

Global estimates of the incidence of PPCM vary by regions, with reports as high as 1 in 100 deliveries in Nigeria (6) and 1 in 300 deliveries in Haiti (7), to as low as 1 in 20,000 deliveries in Japan (8). In the United States, reported incidence ranges from 1 in 1,000 to 1 in 4,000 (9–11) and may be increasing, due to the rise in maternal age, increased rates of multifetal pregnancies due to contemporary fertility techniques, and possibly to increased recognition of the disease. Many cases may moreover be unrecognized; thus, the true incidence is unknown.

RISK FACTORS

Several risk factors have been associated with PPCM. The incidence of PPCM is higher in women of African ancestry (10,12–15). In nationwide studies from the United States, >40% of the cases occurred in African-American women (9,10,16). Similarly, statewide studies report PPCM occurring 3 to 16 times as often in African-American women compared with white women (12–14). Pre-eclampsia and hypertension are strongly associated with PPCM (3,10,14,17–19). A meta-analysis of 22 studies including 979 cases of PPCM reported that pre-eclampsia was present in 22% of women with PPCM, compared with an average worldwide background rate of 5%, and other hypertensive disorders were present in 37% (18). Hypertension and pre-eclampsia can lead to HF and pulmonary edema due to predominant LV diastolic dysfunction. Although subclinical LV systolic dysfunction can be detected by speckle tracking strain imaging, LVEF is preserved (20–24). The majority of women with pre-eclampsia do not develop PPCM, which is only diagnosed when the systolic function is decreased. Multigestational pregnancies are reported in 7% to 14.5% of women with PPCM in the United States (17,18,25,26). A meta-analysis of 16 studies of PPCM showed an overall incidence of twin pregnancies in 9% of women, compared with the national average of 3% (18). Older maternal age also appears to be associated with PPCM (3,12,14): one-half of cases of PPCM occur in women age >30 years, and 1 study reported that age >40 years had an odds ratio of 10 of developing the disease compared with women age <20 years (9). Although a minority of women with PPCM have a family history of cardiomyopathy (see the Genetics section), awareness of HF symptoms during and after pregnancy may improve detection of PPCM in these patients. Closer surveillance of women who are at highest risk during pregnancy could lead to earlier diagnosis and treatment.

PATHOPHYSIOLOGY

The etiology of PPCM is not fully understood and is likely multifactorial. Suggested but not proven mechanisms for the development of PPCM have included nutritional deficiencies (27,28), viral myocarditis (29,30), and autoimmune processes (31,32). Hemodynamic stress of pregnancy has been postulated as a potential etiology. However, the maximal cardiovascular changes occur in the second trimester (33), when most women with pre-existing cardiac disease develop symptomatic HF (34). In contrast, the majority of women with PPCM develop symptoms during late pregnancy or after the delivery (35).

The development of 2 vascular-hormonal animal models of pregnancy-associated cardiomyopathy suggested novel mechanisms for PPCM in humans. The first model was a STAT3 knockout mouse in which oxidative stress led to cleavage of the nursing hormone, prolactin. The 16-kDa prolactin fragment had vasculotoxic and pro-apoptotic properties and vascular and myocardial dysfunction (36). The mice treated with bromocriptine, a suppressor of prolactin secretion, had complete reversal of the

CENTRAL ILLUSTRATION **Diagnosis, Management, and Outcomes for Peripartum Cardiomyopathy**

Peripartum Cardiomyopathy (PPCM)

Definition:

- Non-ischemic cardiomyopathy with reduced LVEF (<45%)
- Commonly presents in the first months postpartum or towards the end of pregnancy

Risk Factors:

- African-American race, preeclampsia, hypertension, multigestational pregnancies, age >30 years

Symptoms:

- Heart failure symptoms can be confused with common symptoms of normal pregnancy

Management Options for PPCM

During Pregnancy:

- Beta-blockers, loop diuretics, hydralazine/isosorbide dinitrate, digoxin, low-molecular-weight heparin
- (No ACE/ARB/aldosterone receptor antagonists)
- MCS for severe heart failure/cardiogenic shock
- Consider early delivery if unstable

Delivery:

- Plan ahead with a Cardio-Obstetrics Team
- If unstable, consider hemodynamic monitoring and optimization
- Caution for fluid overload, especially after delivery

After Pregnancy:

- Heart failure management. Beta-blockers, enalapril, and spironolactone are compatible with breastfeeding.
- Anticoagulation for LV thrombus; consider if severe LV dysfunction (LVEF <35%)
- Consider a wearable cardioverter/defibrillator if severe LV dysfunction
- Discuss Contraception

Outcomes

Worse prognosis with lower LVEF, dilated LV, African-American race, and delayed diagnosis.

Long-term Outcomes

- After recovery, optimal duration of medication treatment is unknown
- In the case of stopping medications, wean gradually and observe closely
- Continue surveillance after recovery

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Diagnostic criteria, symptoms, and risk factors can aid in the diagnosis. Medications need to be tailored to pregnancy and breastfeeding status. Short- and long-term outcomes are variable and serial follow-up is important. ACE = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; LV = left ventricle; LVEF = left ventricular ejection fraction; MCS = mechanical circulatory support; PPCM = peripartum cardiomyopathy.

cardiomyopathy. Of note, human prolactin has been shown to be more resistant to cleavage than prolactin in rats (37), and extrapolations from rodent models may be limited. A second vascular-hormonal mouse model of PPCM was developed by cardiac-specific genetic deletion of proliferator-activated receptor-gamma coactivator-1a (PGC-1a), leading to vasculotoxicity by activation of the 16-kDa prolactin fragment and decreased expression of proangiogenic vascular endothelial growth factor (VEGF). In this model, the cardiomyopathy could be reversed only partly with bromocriptine and required the addition of VEGF for complete recovery (38). VEGF is also strongly antagonized in late gestation by the placental secretion of soluble Fms-like tyrosine kinase 1 (sFlt1), an antagonist of VEGF and placental growth factor. Exogenous sFlt1 was sufficient to cause profound systolic dysfunction in mice lacking cardiac PGC-1 alpha, even in the absence of pregnancy. Moreover, sFlt1 levels are markedly elevated in women with preeclampsia, likely in part explaining why preeclampsia is such a strong risk factor for PPCM. Elevated sFlt1 levels have also been found in a subset of women with PPCM and predict worse outcomes (39). In summary, 2 mouse models and epidemiological data support the notion that PPCM is in large part a vascular disease, triggered by the hormonal milieu of the peripartum (40,41).

GENETICS

Genetic differences may explain why only relatively few women develop HF in response to the vascular insults of late pregnancy. Observations of familial clustering of PPCM, as well as ~6% co-occurrence with idiopathic dilated cardiomyopathy (DCM), suggested early on the possibility of a genetic contribution to the disease (42–48). In a German registry, 15% of women with PPCM had a family history of cardiac disease in a first-degree relative (defined as PPCM, DCM, sudden death, or arrhythmias) (49). Genetic studies have subsequently supported the notion that genetics contribute to PPCM. A genome-wide association study of 79 patients with PPCM identified a single-nucleotide polymorphism near the *PTHLH* gene (50), and this gene may regulate vascular homeostasis (51). Evaluation of rare pedigrees that include both PPCM and DCM identified likely pathogenic variants in genes known to contribute to DCM such as *TTN* and *BAG3*. In a definitive genetic study of 172 patients with PPCM not pre-selected for family history, targeted sequencing of 43 genes known to associate with DCM revealed a 15% prevalence of truncating variants (i.e., nonsense, missense, or splicing variants) in patients with PPCM (52). Two-thirds of the truncating variants were in the *TTN* gene, with the majority of these in the A band of *TTN*. The *TTN* gene encodes the largest human protein, titin, a critical structural component of sarcomeres in cardiac and skeletal muscle. The prevalence and location of these mutations in *TTN* overlap with other forms of DCM, again suggesting a genetic overlap between these 2 diseases. In post hoc analyses, TTN variants identified in the well-characterized subset of patients derived from the IPAC (Investigations of Pregnancy Associated Cardiomyopathy) cohort correlated with lower LVEF at 1 year, suggesting that the presence of TTN truncating variant may presage worse outcome (52). Overrepresentation of TTN truncating variants have likewise been identified in cohorts of cardiotoxicity associated with chemotherapy (53) and alcohol use (54), suggesting that pregnancy may similarly represent a "second hit" for patients predisposed by genetic variance. Importantly, however, >90% of individuals with TTN truncating variants do not develop DCM or PPCM (55), indicating that additional environmental, genetic, or epigenetic factors are at play. The fact that most women with PPCM do not have a family history of cardiomyopathy and that PPCM does not always recur with a subsequent pregnancy indicates that any genetic origin is incompletely penetrant and that additional factors contribute to disease incidence. Further research in diverse populations is needed to study the interaction of genetic variants with comorbidities as well as vascular, hormonal, and hemodynamic insults.

DIAGNOSIS

TIMING AND CLINICAL PRESENTATION. The majority of women with PPCM are diagnosed after delivery, typically in the first month postpartum (3). Frequent delays in diagnosis occur due to under-recognition of this disease and the overlap in signs and symptoms of normal pregnancy with those of HF. Unfortunately, delays in diagnosis are associated with increased incidence of preventable complications and worse outcomes (3,56,57). Most women present with signs and symptoms of HF including shortness of breath on exertion, fatigue, orthopnea, paroxysmal nocturnal dyspnea, edema, and chest tightness. Physical examination often reveals tachypnea, tachycardia, elevated jugular venous pressure, pulmonary rales, and peripheral edema. A minority of patients will present with cardiogenic shock, severe arrhythmias, and thromboembolic complications.

DIAGNOSTIC TESTING. Echocardiography should be performed in any suspected case of PPCM as the

TABLE 1 Differential Diagnosis for Heart Failure During Pregnancy

Differential Diagnosis	Considerations
Takotsubo cardiomyopathy	Echocardiogram may show classic apical ballooning
Familial cardiomyopathy	Family history, genetic testing
Pre-existing cardiomyopathy	History of HF prior to pregnancy; prior echo studies with low LVEF before pregnancy
Recurrent peripartum cardiomyopathy	Ask about symptoms of HF that occurred after a prior pregnancy
Pre-eclampsia	Preserved systolic function on echocardiogram
Hypertrophic cardiomyopathy	Left ventricular hypertrophy, LVOT obstruction, preserved systolic function, genetic testing
Myocarditis	Consider if viral prodrome, histological diagnosis, fulminant presentation
Arrhythmogenic right ventricular cardiomyopathy	Consider with family history, genetic testing, echocardiographic findings
Left ventricular noncompaction	Echocardiographic and CMR findings
Chemotherapy-related cardiomyopathy	History of chemotherapy, particularly doxorubicin
Valvular heart disease	Echocardiographic findings; congenital aortic stenosis; mitral stenosis from rheumatic heart disease in endemic country. Patients with PPCM may also have valve disease, i.e., mitral regurgitation
Congenital heart disease	May be diagnosed for the first time during pregnancy by echocardiography
Tachycardia-arrhythmia mediated cardiomyopathy	Consider if specific underlying rhythm abnormality. Note that sinus tachycardia may be secondary to heart failure during pregnancy
Hypertensive heart disease	Left ventricular hypertrophy; less common in young people unless very longstanding history of hypertension
Ischemic heart disease	Cardiovascular risk factors; angina; prior CAD; consider SCAD and MINOCA diagnoses
Cardiomyopathy related to other systemic medical diseases	Consider in the appropriate context, i.e., systemic lupus erythematosus, antiphospholipid syndrome, hemochromatosis
Cardiomyopathy related to other acute conditions	May consider if patient has other conditions such as sepsis, treatment in intensive care unit, post-respiratory arrest
Pulmonary embolism	Dyspnea, tachycardia with preserved LVEF

CAD = coronary artery disease; CMR = cardiac magnetic resonance imaging; HF = heart failure; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; MINOCA = myocardial infarction in non-obstructive coronary arteries; PPCM = peripartum cardiomyopathy; SCAD = spontaneous coronary artery dissection.

LVEF is typically <45% (4). In addition to systolic dysfunction, the echocardiogram may demonstrate LV and right ventricular dilatation and/or dysfunction, functional mitral and/or tricuspid regurgitation, pulmonary hypertension, and left atrial or biatrial enlargement. Intracardiac thrombus may occur (17,58), and the LV apex should be clearly visualized particularly when the LVEF is severely reduced. Levels of brain natriuretic peptide (BNP) and N-terminal pro-BNP, which do not change significantly during normal pregnancy and may be mildly elevated in the setting of pre-eclampsia, are usually markedly elevated in PPCM (59-62). The electrocardiogram may show nonspecific abnormalities, but a normal electrocardiogram does not rule out PPCM (63). Chest x-rays show pulmonary venous congestion. Cardiac magnetic resonance imaging provides accurate ejection fraction and chamber measurements when the echocardiogram is inadequate, but gadolinium is avoided during pregnancy. Endomyocardial biopsy is only indicated if there is suspicion for an alternative diagnosis, such as giant cell myocarditis, that would necessitate a different management plan.

DIFFERENTIAL DIAGNOSIS. PPCM is a diagnosis of exclusion. To avoid overdiagnosis, careful attention to possible pre-existing heart disease including cardiomyopathies and valvular disease is important. Severe pre-eclampsia can cause HF related to diastolic dysfunction, but PPCM is only diagnosed in the presence of systolic dysfunction. Potential causes of pregnancy-related HF are listed in **Table 1**.

PROGNOSIS AND OUTCOMES

ADVERSE OUTCOMES. PPCM is associated with adverse outcomes, including brain injury, cardiopulmonary arrest, pulmonary edema, thromboembolic complications, mechanical circulatory support, cardiac transplantation, and death. In a study of 182 women with PPCM, the major adverse event preceded the diagnosis of PPCM in one-half of the patients, and cerebrovascular events and cardiopulmonary arrest were associated with residual brain damage (57). LV thrombus has been identified in as much as 10% to 17% of initial echocardiograms (17,64), and thromboembolic complications have been reported in 5% to 9% of women (65,66). The increased incidence of thromboembolic events in PPCM is likely related to the hypercoagulable state of pregnancy, cardiac dilatation and dysfunction, venous stasis, bed rest, and the post-operative status after cesarean section.

PROGNOSTIC FACTORS. Of various prognostic factors that have been studied, LVEF at the time of diagnosis is the most reliable predictor of adverse events or long-term recovery (3,25,57,67–69). In the IPAC cohort, LVEF <30% was associated with lower rates of recovery and increased risk of adverse events (70). Despite severe LV dysfunction at the time of diagnosis, some women will recover; thus, initial LVEF is not sufficient for determining an early and possible premature need for advanced therapies such as durable left ventricular assist device (LVAD), implantable cardioverter-defibrillator (ICD), cardiac resynchronization therapy, or transplant (25). Additional predictors of worse outcome include LV dilatation (17,25,67,70–72), LV thrombus (17), right ventricular systolic dysfunction (73,74), and obesity (75). African-American ethnicity is strongly associated with lower rates of recovery, longer recovery time, more adverse outcomes, and higher mortality (14,15,70,76). Concomitant pre-eclampsia has been associated with lower 1-year survival, but higher rates of LV recovery in survivors (77). Biomarkers associated with adverse outcomes include troponin (78), NT-proBNP (79), and sFlt1 (39). The presence of late gadolinium enhancement by cardiac magnetic resonance imaging may indicate fibrosis associated with less myocardial recovery; however, most patients with PPCM do not demonstrate late gadolinium enhancement (80,81).

MORTALITY. Mortality estimates differ significantly based on racial groups, geographical region, and duration of follow-up. At 1-year follow-up, mortality rates in the United States ranged from 4% in the IPAC study (70) to 11% in a population of 96% African-American women (82). Two-year mortality rates have been reported as 0% to 16% in different studies in the United States (3,64,68), 15% in Haiti (7), and 28% in Africa (83). Less data are available about long-term outcomes (>5 years), but U.S. mortality estimates have ranged from 7% to 20% (mean follow-up 6.3 to 8.6 years) (14,84–86).

RECOVERY. PPCM has been associated with a higher rate of recovery than other forms of HF with reduced LVEF (64), and recovery frequently occurs within the first 3 to 6 months (3,17,70). Delayed recovery can also occur, even up to 2 years following diagnosis (68,85–88). In the United States, recovery rates have varied depending on the patient population and the definition of recovery. Of the 100 prospectively enrolled women in the IPAC study, 72% recovered to LVEF >50% at 12 months (70). A lower recovery rate (45%) was reported in a study of 55 patients (51% African-American) at follow-up time of 29 months (17), and among 40 indigent patients (87.5% African-American) where only 35% recovered with an average time of 54 months (68). A recent retrospective analysis of 59 women reported 43% recovered to LVEF of ≥50% by 12 months with a median time to recovery of 8 months (86).

MANAGEMENT

MEDICAL MANAGEMENT. Treatment of HF during pregnancy requires special modifications to ensure fetal safety. Following delivery, most HF medications are compatible with breastfeeding (**Figure 1**) (89–95).

Anticoagulation. Due to reports of increased incidence of LV thrombi and systemic thromboembolism in women with PPCM (9,40,57,96) and the hypercoagulable state of pregnancy and the early postpartum period (97), anticoagulation should be considered in the setting of severely decreased LVEF during late pregnancy and 6 to 8 weeks postpartum (40). Anticoagulation is suggested by the American Heart Association when the LVEF is <30% (98), whereas the European Society of Cardiology suggests using LVEF ≤35% as the threshold (99). No published data are available to guide the decision of therapeutic versus prophylactic anticoagulation. Warfarin crosses the placenta and is avoided during pregnancy for indications other than anticoagulation of mechanical heart valves. Low-molecular-weight heparin does not cross the placenta and can be used during pregnancy (92). Both warfarin and low-molecular-weight heparin are considered safe with lactation. The novel anticoagulants have not been studied during pregnancy or lactation and are generally avoided.

EXPERIMENTAL TREATMENT. Bromocriptine is a dopamine agonist and inhibits the release of prolactin. It was originally marketed for lactation suppression, but due to the association with myocardial infarction (100–103), stroke (104,105), and seizures (105), it is no longer approved for this indication. The concept that PPCM is driven by the antiangiogenic and proapoptotic 16-kDa form of prolactin led to experimentation using bromocriptine to inhibit prolactin secretion to prevent the development of PPCM in a mouse model (36). A pilot study compared the outcome of 10 South African patients with PPCM receiving bromocriptine in addition to standard HF therapy to that of 10 patients receiving standard therapy alone (106). Patients treated with bromocriptine (2.5 mg twice daily for 2 weeks, followed by 2.5 mg daily for 6 weeks) had greater improvement in LVEF at 6 months (27% to 58%; $p = 0.012$) than the

FIGURE 1 **Heart Failure and Anticoagulant Medications: Indications and Safety in Pregnancy and During Lactation**

MEDICATION	DURING PREGNANCY	POTENTIAL ADVERSE EFFECTS	INDICATIONS	DURING LACTATION
HEART FAILURE MEDICATIONS				
Loop diuretics	Yes	Caution for hypovolemia or hypotension that may lead to decreased placental perfusion	For signs and symptoms of congestion and fluid overload.	Yes, but over-diuresis can lead to decreased milk production.
Beta blockers (metoprolol tartrate used most commonly)	Yes	IUGR; fetal bradycardia and hypoglycemia	For standard treatment of HF; consider treatment of women with subsequent pregnancy.	Yes
Hydralazine/nitrates	Yes	Caution with hypotension	Use for afterload reduction during pregnancy (instead of ACE-I/ARB) when needed.	Yes, but ACE-I/ARB typically chosen post-partum
Digoxin	Yes	No associated congenital defects	Can be used with symptomatic heart failure and/or systolic dysfunction during pregnancy, or afterwards per guidelines.	Yes
ACE-I/ARB	No	Anuria, oligohydramnios, fetal limb contractures, craniofacial deformation, pulmonary atresia, fetal hypocalvaria, intra uterine growth restriction, prematurity, patent ductus arteriosus, stillbirth, neonatal hypotension and death	Cannot use during pregnancy. After delivery, should be used as part of guideline-directed medical therapy for afterload reduction and LV remodeling.	Enalapril and captopril can be used
Aldosterone receptor antagonists	No	Spironolactone has been associated with antiadrenergic activity, feminization of male rat fetuses and permanent changes in reproductive tract in both sexes	As per guideline-directed medical therapy for heart failure.	Spironolactone can be used
Sacubitril-valsartan	No	Same as ACE-I/ARB	As per guideline-directed medical therapy for heart failure.	No information in human, present in rat milk
Ivabradine	Scant data in humans; would avoid due to concerns in animal studies	Scant data in humans, animal data suggest risk	As per guideline-directed medical therapy for heart failure.	No information in human, present in rat milk
ANTICOAGULANTS				
Low molecular weight heparin	Yes	Caution at time of delivery and with neuraxial anesthesia; does not cross placenta; consider the need for monitoring anti-Xa levels	For prevention and treatment of thromboembolic complications during pregnancy and as bridge to warfarin postpartum.	Yes
Warfarin	Avoid	Warfarin embryopathy and fetopathy	For prevention and treatment of thromboembolic complications postpartum.	Yes

Legend:

	Data or experience to support use
	Caution with using this medication
	Data is limited or inconclusive

Safety of medications need to be considered during pregnancy and lactation. ACE-I = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blocker; HF = heart failure; IUGR = intra-uterine growth restriction; LV = left ventricular; SSP = subsequent pregnancy.

control group (27% to 36%), and fewer experienced the composite endpoint (n = 1, 10%) (defined as death, New York Heart Association functional class III/IV, or LVEF <35% at 6 months) compared with the control group (n = 8, 80%; p = 0.006). A second African study compared the outcome of 48 patients with PPCM receiving HF therapy of furosemide and angiotensin-converting enzyme (ACE) inhibitors to an equal number of patients additionally receiving bromocriptine 2.5 mg twice daily for 4 weeks (107). LVEF was similar at entry but higher in the bromocriptine group at 2 weeks (p = 0.01) and at 3, 6, and 12 months (p = 0.001). Mortality at 6 months was high in both groups but lower in the bromocriptine-treated women (17% vs. 29%; p = 0.0001). The results of these 2 African studies and their general applicability were limited by the uncharacteristically high mortality rate in the control group compared with other studies (108). An observational registry of 115 German patients with PPCM reported that bromocriptine in addition to standard therapy was associated with a higher rate of improvement in LVEF, but there was no significant difference in overall rates of recovery (49). Recently, a randomized trial of 2 different regimens of bromocriptine (1 week in 27 patients vs. 8 weeks in 31 patients) in Germany found similar outcomes in both groups (109). Treatment was started on the average of 1.6 ± 1.6 months after the delivery, in addition to standard HF therapy including ACE inhibitors/angiotensin receptor blockers, beta-blockers, mineralocorticoid antagonists, and diuretic agents. The investigators postulated an association between bromocriptine and the favorable outcomes, but the absence of a control group not receiving bromocriptine makes the results inconclusive. No information is available for the use of this therapy in women with PPCM in the United States. Until more definitive information becomes available, bromocriptine should be considered experimental. The implications of not breastfeeding due to bromocriptine should be discussed with the patient. A randomized double-blind, placebo control study (REBIRTH [Randomized Evaluation of Bromocriptine In Myocardial Recovery Therapy]) to investigate the effect of bromocriptine on myocardial recovery and clinical outcome of 200 women with PPCM in the United States and Canada has been proposed by the IPAC group and is under evaluation. The 2018 European Society of Cardiology guidelines include a weak recommendation (Class IIb, Level of Evidence: B) for the use of bromocriptine (110). Due to the association with thrombotic complications, therapeutic anticoagulation is recommended in conjunction with bromocriptine.

TREATMENT OF SEVERE PPCM. Intravenous vasodilators, such as nitroglycerin, may be needed in the setting of acute decompensated HF during pregnancy. Nitroprusside is less desirable due to the theoretical risk of cyanide toxicity (92). Possible adverse effects of dobutamine were described in an observational study of 27 nonrandomized patients with PPCM and LVEF ≤25% (111). The 7 women treated with dobutamine had worse outcomes, but there may have been selection bias in this small study. Levosimendan is an alternative inotropic medication (99), but was not shown to improve outcomes in a randomized study of 24 patients with PPCM (112), and is not available in the United States or Canada. A recent comparison of milrinone and levosimendan in 15 women with PPCM showed comparable hemodynamic improvement with both drugs (113).

Advanced therapies. A total of 60% of cases of cardiogenic shock during or shortly after pregnancy are caused by PPCM (114). Temporary mechanical circulatory support with intra-aortic balloon pump, percutaneous ventricular assist device therapy, and extracorporeal membrane oxygenation have been used successfully in PPCM and should be considered early in patients with hemodynamic instability despite inotropic support (115–119). Temporary or durable LVADs may also be needed. Of 99 women with PPCM who received LVAD, 6% recovered and 48% went on to cardiac transplantation (118). A study of 485 women with PPCM who received cardiac transplant between 1987 and 2010 reported higher rates of graft failure and lower age-adjusted survival, which may be explained by increased rejection, higher allosensitization, and higher pre-transplant acuity (120).

LABOR AND DELIVERY. Timing and mode of delivery in patients presenting with PPCM during pregnancy should be discussed with the patient and coordinated by a cardio-obstetrics team of experts from obstetrics, cardiology, maternal fetal medicine, anesthesiology, nursing, pharmacy, and social work (121). An attempt to stabilize the mother to avoid potential fetal complications of prematurity is reasonable. Hemodynamic instability despite medical therapy should prompt early delivery (or termination if prior to fetal viability). Stable patients are delivered vaginally unless there are obstetric reasons for cesarean section. Cesarean delivery is associated with a higher incidence of hemorrhage, infection, and thromboembolic complications (122). Detailed pre-delivery plans should involve the patient and an experienced multidisciplinary team. Unstable patients may benefit from invasive hemodynamic optimization prior to

FIGURE 2 Counseling and Management of Subsequent Pregnancies in PPCM

Subsequent Pregnancy	Recovered (LVEF ≥50%)	Nonrecovered (LVEF <50%)
Preconception or First Visit	Preconception risk counseling and follow-up planning. Clinical and LVEF reassessment off renin-angiotensin blocking agents for 3 months. Baseline echocardiogram and BNP/NT-proBNP level.	Preconception risk counseling including discussion of alternative ways to build a family. If pregnant and not considering termination: Close follow-up planning, stop renin-angiotensin blocking agents and switch to hydralazine/isosorbide dinitrate. Baseline echocardiogram and BNP/NT-proBNP level.
Maternal Risks	~20% have a relapse Severe deterioration is rare Mortality unlikely Rate of subsequent recovery is high	Higher risk of relapse ~50% show further deterioration in LV dysfunction Increased morbidity and mortality Premature delivery and abortion more common
Medications	Continue beta blocker therapy (metoprolol tartrate preferred). Yield of starting prophylactic beta blocker therapy unclear. Diuretics and hydralazine/isosorbide dinitrate in case of clinical or LV functional deterioration.	Continue beta blocker therapy (metoprolol tartrate preferred). Hydralazine/Isosorbide dinitrate for hemodynamic and symptomatic improvement. Consider digoxin. Consider anticoagulation if severe LV dysfunction (LVEF <35%).
Follow-up	Close monitoring of symptoms during pregnancy and the postpartum period with repeat echocardiographic assessment of LV function and BNP/NT-proBNP level at the end of the 1st and 2nd trimesters, 1 month prior to delivery, after delivery prior to hospital discharge, 1 month postpartum, and at any time if symptoms develop.	
Labor and Delivery	Multidisciplinary team for planning; patient involved. Spontaneous vaginal delivery preferred unless fetal or maternal instability. Monitor for volume overload in the first 48 hours after delivery in cases of recurrent LV dysfunction.	Multidisciplinary team for planning; patient involved. Spontaneous vaginal delivery preferred unless fetal or maternal instability. Early delivery if further decrease in LV function and hemodynamic deterioration. Consider hemodynamic monitoring for optimization prior to delivery and monitoring during and after delivery. Monitor for volume overload in the first 48 hours after delivery.

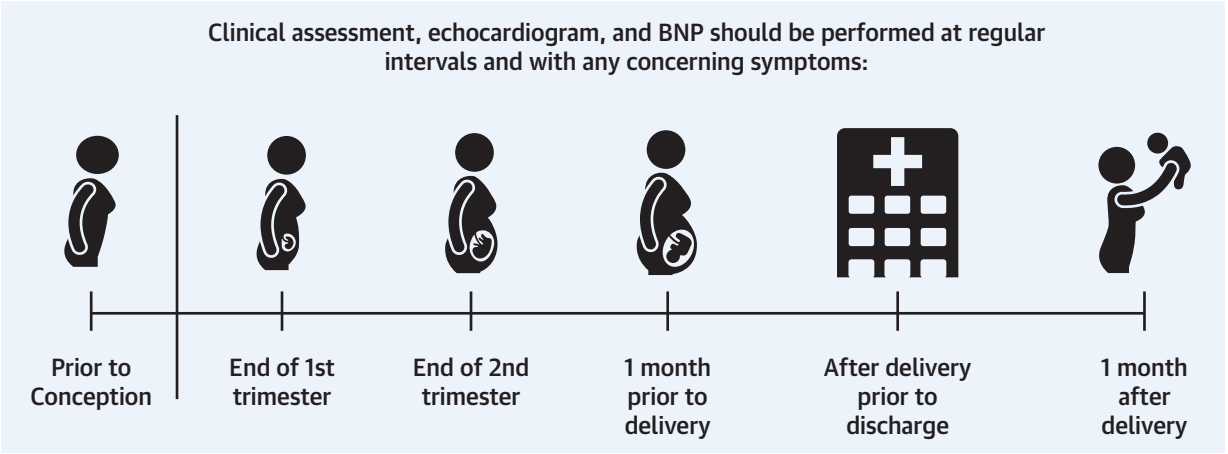
Risks of a subsequent pregnancy differ based on the pre-conception recovery status. There is higher risk with nonrecovered myocardial function and pregnancy should be discouraged. Peripartum management options depend on the clinical status and myocardial function. ACE = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; LV = left ventricular; LVEF = left ventricular ejection fraction; PPCM = peripartum cardiomyopathy.

delivery and monitoring during delivery and the early postpartum period. Following delivery, removal of caval compression by the fetus, autotransfusion due to uterine contractions, and fluid mobilization and resorption contribute to an increase in venous return. The post-partum risk of fluid overload and pulmonary edema must be anticipated.

PRIOR TO HOSPITAL DISCHARGE

LACTATION. Breastfeeding confers multiple benefits for infants and mothers (123,124) and is recommended by the World Health Organization and the American Academy of Pediatrics (125). In developing countries where formula may be expensive and clean

FIGURE 3 Serial Monitoring During a Subsequent Pregnancy


Clinical assessment, echocardiogram, and BNP should be performed at regular intervals and with any concerning symptoms:
Prior to Conception
End of 1st trimester
End of 2nd trimester
1 month prior to delivery
After delivery prior to discharge
1 month after delivery

Proposed outline for serial testing during a subsequent pregnancy. BNP = brain natriuretic peptide.

water is not readily available, not breastfeeding can pose a significant risk to the infant (126). Based on the prolactin hypothesis, the 2010 European statement on PPCM advised against breastfeeding (4). However, a small study of patients enrolled online in the United States indicated that women who breastfed actually had higher rates of recovery (26). Recent data from IPAC demonstrated that breastfeeding was not associated with adverse outcomes, inflammatory markers, or persistent myocardial dysfunction (127). The observation that breastfeeding seems to be safe in PPCM suggests that continued stimulation of prolactin secretion may not be harmful (128). Most HF medications can be given safely with breastfeeding (**Figure 1**) and should not be a reason to advise women against lactation.

SUDDEN DEATH PREVENTION. Only limited published data is available to guide the timing of ICD placement in women with PPCM. Premature placement should be avoided because a large proportion of women will recover to LVEF >35% within the first 6 months postpartum and will not meet criteria for ICD placement (129). Unfortunately, women with PPCM may experience cardiac arrest in the early months following diagnosis (130) and need to be protected. A recent analysis of administrative data of 9,841 hospitalizations with a primary diagnosis of PPCM revealed that 18.7% had an arrhythmia; of these, 4.2% had ventricular tachycardia, 1% had ventricular fibrillation, and 2.2% had cardiac arrest (131). In a small prospective study of women with newly diagnosed PPCM, 3 of 7 patients with severely reduced LVEF who were compliant with a wearable cardioverter/defibrillator were found to have ventricular fibrillation that was appropriately shocked (130). A subsequent retrospective multicenter study by the same group reported that of 49 women with newly diagnosed PPCM and LVEF <35%, 12% (n = 6) had ventricular tachyarrhythmias (5 episodes of ventricular fibrillation, 2 with sustained ventricular tachycardia, and 1 with nonsustained ventricular tachycardia), and there were no inappropriate shocks (132). In contrast, a retrospective analysis of wearable cardioverter/defibrillators in 107 patients with PPCM found no shocks were delivered (either appropriate or inappropriate) during an average of 4 months of follow-up (133). Thus, despite conflicting data in small studies, and until more information becomes available, it may be reasonable to consider wearable cardioverter/defibrillators for women with new onset PPCM and severe LV dysfunction as a bridge to recovery or until an implantable ICD is indicated. Certain patients may benefit from cardiac resynchronization therapy. An anecdotal report demonstrated positive remodeling and improvement in LVEF in 2 women with PPCM treated with CRT after failing to improve on medical therapy (134).

CONTRACEPTION. Contraception should be discussed at the time of diagnosis or prior to hospital discharge. In the early postpartum setting with severe LV dysfunction, the increased risk of thromboembolism should dissuade the use of estrogen-containing

contraceptives. Progesterone-releasing subcutaneous implants or the Mirena intrauterine device are safe and effective choices. Injectable depot medroxyprogesterone acetate is less effective and is considered a second-line option. Nonhormonal barrier methods are less effective. Tubal ligation and vasectomy are other options. In a woman with persistent LV dysfunction, the risk of a subsequent pregnancy likely outweighs any risk associated with contraception. Therefore, women should be encouraged to select the method they will use most consistently. The importance of contraception should be emphasized by the cardiologist, as well as the obstetrician/gynecologist (135).

DURATION OF TREATMENT. In the presence of persistent cardiac dysfunction, cardiac medications should be continued indefinitely. After LV recovery, optimal duration of treatment is unknown. A rationale for continuation of medical therapy is supported by evidence of subclinical LV systolic dysfunction and anecdotal reports of late deterioration of LV function. Impaired LV global longitudinal and apical circumferential 2-dimensional strain were reported in 29 women with LV recovery (defined as LVEF ≥50%) at least 12 months after acute PPCM (136), supporting prior reports of decreased contractile reserve on dobutamine stress echocardiogram in women with PPCM and recovered LVEF (137). In addition, anecdotal reports have described deterioration of LV function after partial or complete recovery, even in the absence of a subsequent pregnancy (57,86,138). A recent study of patients with recovered DCM (LVEF >50%) not related to pregnancy reported that 44% needed to restart cardiac medications within 6 months after discontinuation (139). It is not clear whether these findings can be extrapolated to patients with PPCM. If the patient is free from congestive symptoms, diuretic medications can be stopped. Additional HF medications, if stopped, should be weaned in a stepwise fashion with frequent clinical assessment and echocardiographic monitoring of LVEF (i.e., every 3 to 6 months). Reassessment of LV function is advised after drug discontinuation followed by annual clinical and echocardiographic assessment.

SUBSEQUENT PREGNANCY

The safety of a subsequent pregnancy is a frequent concern for patients and their families. Appropriate and accurate counseling is essential. The risks associated with a subsequent pregnancy depend primarily upon whether the myocardial function has fully recovered, and the pre-pregnancy LVEF is the strongest predictor of outcomes (**Figure 2**). Detection of subclinical LV dysfunction by stress testing and strain imaging has been proposed (136,140), but further research about the predictive utility of these tests is needed.

RESIDUAL MYOCARDIAL DYSFUNCTION. If there is evidence of persistent myocardial dysfunction (i.e., LVEF <50%), women should be advised on the reported high risk of recurrent HF, durable deterioration of cardiac function, and mortality. In a review of 93 women with persistent LV dysfunction (published between 2001 and 2010), nearly one-half had deterioration of LV function, which persisted in 39%, and 16% died (141). A more recent study of 16 European and African women with LV dysfunction prior to a subsequent pregnancy reported death in 25%, and only 31% recovered LV function >50% (142). Additionally, fetal outcomes tend to be worse among women with persistent LV dysfunction, with higher rates of stillbirth, abortion, and pre-term delivery (141). Based on these data, the 2018 European Society of Cardiology guidelines for the management of cardiovascular diseases during pregnancy discourage subsequent pregnancy if the LVEF is not >50% to 55% (110). After counseling, some women choose to proceed and should be followed closely during pregnancy.

RECOVERED MYOCARDIAL FUNCTION. Women who recover LVEF >50% have lower risk of complications during a subsequent pregnancy, but there is still increased risk of recurrent HF (141). An early study of 23 subsequent pregnancies in women with recovered LVEF reported no deaths, but 21% had a substantial (>20%) decrease in LVEF and symptoms of HF, with 14% having persistent LV dysfunction (143). A prospective study of 18 women with subsequent pregnancies in Europe and Africa reported no mortality but an average of 15% reduction in LVEF after the delivery, which was persistent in almost one-half of them (142). More recently, a single-center study in the United States of 39 pregnancies in 24 women with LVEF of ≥50% prior to subsequent pregnancy reported no maternal deaths and a relapse rate of 21% (LVEF nadir range of 35% to 45%) (144). All patients were reported to recover, although 3 women required admission to the intensive care unit. None of these patients were treated with bromocriptine, 79% breastfed their infants, and 44% were treated with beta-blockers (144). Pre-conception counseling should include discussion of the potential risk of recurrent myocardial dysfunction, which may persist after the pregnancy.

MONITORING AND TREATMENT DURING SUBSEQUENT PREGNANCY. Our recommended protocol for monitoring women with a history of PPCM during a subsequent pregnancy is outlined in **Figures 2 and 3**. In women with recovered LV function who are taking HF medications, ACE inhibitors/angiotensin receptor blockers, and aldosterone receptor antagonists should be discontinued prior to conception, and it may be prudent to ensure stability of LV function after at least 3 months off of these medications prior to considering the LV recovered. The prophylactic use of beta-blockers during subsequent pregnancies in women with recovered LVEF may be considered but there is a paucity of data to support its role. In the study by Codsi et al. (144), 19 of 43 women with subsequent pregnancies were treated with beta-blockers, 6 had a decrease in LVEF, and there were no instances of intrauterine growth restriction. In a recent series of patients with subsequent pregnancies, it was postulated that addition of bromocriptine to standard therapy led to higher rates of recovery and no deaths (142); however, this was a small, nonrandomized study, and there was a significant difference in the baseline LVEF in the 2 arms of the study.

CONCLUSIONS

The diagnosis of PPCM should be considered in any pregnant or postpartum woman with symptoms concerning for HF. An elevated BNP level should always be followed by an echocardiogram to assess for systolic dysfunction. Prompt treatment with medications tailored for pregnancy and lactation may prevent adverse outcomes. Limited studies suggest breastfeeding is safe. Acutely ill women should be managed by specialized multidisciplinary teams, and may require advanced HF therapies. Women considering a subsequent pregnancy should be counseled and monitored by physicians familiar with PPCM. Long-term follow-up is important, but the optimal duration of medications following recovery is unknown.

Despite many advances in our understanding of PPCM, questions remain about the pathogenesis and complex interaction of genetics with the vascular and hormonal milieu of late pregnancy. The role of bromocriptine remains unclear, and randomized clinical trials are needed for determining the risks and potential benefits. Important gaps in knowledge remain, such as the optimal anticoagulation strategy, timing of ICD implantation, risk prediction and management during a subsequent pregnancy, and the long-term duration of medications after myocardial recovery. Given the overall rarity of PPCM, collaboration among multiple centers will be needed to answer these questions.

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